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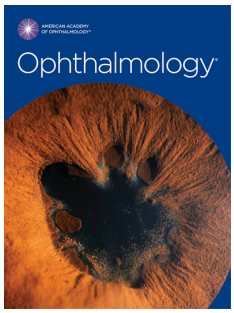

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The Port Delivery System with Ranibizumab for Neovascular Age-Related Macular Degeneration: Results from the Randomized Phase 2 Ladder Clinical Trial

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Supplemental materials: This article contains additional online-only material. The following should appear online-only: Tables S1–S5, Figures S1–S4, Videos S1–S2, Appendices S1–S3.

Previous presentation

Portions of these data were presented at the American Society of Retina Specialists 2018 Annual Meeting, Vancouver, British Columbia, Canada, July 20–25, 2018; the Retina Society 2018 Annual Scientific Meeting, San Francisco, California, September 12–15, 2018; the EURETINA 2018 Congress, Vienna, Austria, September 20–23, 2018; the American Academy of Ophthalmology 2018 Annual Meeting; Chicago, Illinois, October 27–30, 2018; the Bascom Palmer Eye Institute Angiogenesis, Exudation, and Degeneration 2019 Meeting, Miami, Florida, February 9, 2019; the 42nd Annual Macula Society Meeting, Bonita Springs, Florida, February 13–16, 2019; and the EURETINA 9th Winter Meeting, Prague, Czech Republic, March 1–2, 2019.

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Conflict of interest

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Running head
Phase 2 Trial of the Port Delivery System with Ranibizumab

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Abbreviations and Acronyms:
ADA = antidrug antibody; **AE** = adverse event; **BCVA** = best-corrected visual acuity; **CFT** = central foveal thickness; **CI** = confidence interval; **CNV** = choroidal neovascularization; **ETDRS** = Early Treatment Diabetic Retinopathy Study; **HR** = hazard ratio; **ILM** = inner limiting membrane; **MMRM** = mixed-effect model repeated measures; **nAMD** = neovascular age-related macular degeneration; **NA** = not applicable; **NE** = not evaluable; **NI** = noninferiority; **PDS** = Port Delivery System with ranibizumab; **PED** = pigment epithelial detachment; **RPE** = retinal pigment epithelium; **SAE** = serious adverse event; **SD** = standard deviation; **SD-OCT** = spectral domain optical coherence tomography; **VEGF** = vascular endothelial growth factor.

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Abstract

Purpose: To evaluate the safety and efficacy of the Port Delivery System with ranibizumab (PDS) for neovascular age-related macular degeneration (nAMD) treatment.

Design: Phase 2, multicenter, randomized, active treatment–controlled clinical trial.

Participants: Patients diagnosed with nAMD within 9 months who had received ≥ 2 prior anti–vascular endothelial growth factor intravitreal injections and were responsive to treatment.

Methods: Patients were randomized 3:3:3:2 to receive the PDS filled with ranibizumab 10 mg/mL, 40 mg/mL, and 100 mg/mL formulations or monthly intravitreal ranibizumab 0.5 mg injections.

Main Outcome Measures: Time to first implant refill assessed when the last enrolled patient completed the month 9 visit (primary efficacy endpoint); improvement in best-corrected visual acuity (BCVA) and central foveal thickness (CFT); and safety.

Results: The primary analysis population was 220 patients, with 58, 62, 59, and 41 patients in the PDS 10 mg/mL, 40 mg/mL, and 100 mg/mL arms and the monthly intravitreal ranibizumab 0.5 mg arm, respectively. Median time to first implant refill was 8.7, 13.0, and 15.0 months in the PDS 10 mg/mL, 40 mg/mL, and 100 mg/mL arms, respectively. At month 9, the adjusted mean BCVA change from baseline was –3.2, –0.5, +5.0, and +3.9 Early Treatment Diabetic Retinopathy Study letters in the PDS 10 mg/mL, 40 mg/mL, and 100 mg/mL arms and the monthly intravitreal ranibizumab 0.5 mg arms, respectively. At month 9, the adjusted mean CFT change from baseline was similar in the PDS 100 mg/mL and the monthly intravitreal ranibizumab 0.5 mg arms. The optimized PDS implant insertion and refill procedures were generally well tolerated. After surgical procedure optimization, postoperative

vitreous hemorrhage rate was 4.5% (7/157; 1 event classified as serious). There was no evidence of implant clogging.

Conclusions: In the phase 2 Ladder trial, the PDS was generally well tolerated and demonstrated a dose response across multiple endpoints in patients with nAMD. The PDS 100 mg/mL arm had visual and anatomic outcomes comparable with monthly intravitreal ranibizumab 0.5 mg injections, but with a reduced total number of ranibizumab treatments. The PDS has the potential to reduce treatment burden in nAMD while maintaining vision.

Introduction

Intravitreal anti-vascular endothelial growth factor (VEGF) therapy is the accepted standard of care for patients with neovascular age-related macular degeneration (nAMD).[1,2] Despite the documented benefits of anti-VEGF treatment, a great challenge has been translating the vision improvements achieved in clinical trials to patients in real-world clinical practice. In clinical trials, anti-VEGF–treated patients consistently experienced 1- to 2-line vision gains from baseline, with the highest benefit observed in patients who were monitored and treated monthly.[3-7] In contrast, in observational studies tracking patient outcomes in clinical practice, vision gains from baseline are generally limited to < 1 line of vision.[8-13] Part of the gap between clinical trial results and clinical practice outcomes may be a result of the high treatment burden associated with nAMD management and treatment.[14-17] Observational data indicate that patients are monitored and treated less frequently, potentially contributing to the poorer vision outcomes compared with clinical trial results.[3-13] Thus, difficulty with maintaining office visit and injection frequency is a major problem that adversely impacts patient outcomes, and new approaches to prolonged VEGF suppression are needed.

The Port Delivery System with ranibizumab (PDS) is a novel, innovative, long-acting drug delivery system with the potential to reduce treatment burden while maintaining optimal vision outcomes by enabling the continuous delivery of a customized formulation of ranibizumab into the vitreous. The PDS includes a permanent, refillable implant that is surgically inserted through a small incision in the sclera and pars plana. A self-sealing septum in the center of the implant flange allows access to the implant reservoir for drug replenishment without the need to remove the implant from the eye (Fig 1). Ranibizumab moves by passive diffusion down a concentration gradient from the implant reservoir, through a porous metal release control element specifically designed for ranibizumab, and into the

vitreous cavity. This passive diffusion through the release control element results in the controlled continuous release of ranibizumab into the vitreous over time.

A phase 1 study in patients with nAMD demonstrated that the PDS was well tolerated, and secondary outcomes, including change from baseline in best-corrected visual acuity (BCVA) and implant functionality, supported further investigation.[18] The PDS used in the phase 1 study was a prototype that allowed proof-of-concept testing. Subsequently, numerous technical improvements were made to ensure reliability, durability, and drug exchange, and to enable high-volume manufacturability. The phase 2 Ladder trial (ClinicalTrials.gov NCT02510794), whose primary analysis results are reported herein, assessed the safety and efficacy of the technically improved PDS in patients with nAMD responsive to anti-VEGF treatment.

Methods

Study Design

The Ladder trial is an ongoing phase 2, multicenter, randomized, active treatment–controlled, dose-ranging clinical trial of the PDS for nAMD conducted at 49 sites in the United States (see Appendix S1, available at www.aaojournal.org, for full list of investigators and study sites). The trial adhered to the tenets of the Declaration of Helsinki[19] and was conducted in accordance with the International Conference on Harmonisation E6 Guidelines for Good Clinical Practice[20] and with applicable local, state, and federal laws. All trial sites received institutional review board approval before trial initiation and all patients provided written informed consent before enrollment. All results reported herein are for the completed primary analysis.

Study Population

Eligible patients were age ≥ 50 years with anti-VEGF–responsive nAMD in the study eye diagnosed within the 9 months before screening (see Appendix S2, available at www.aaojournal.org). Patients had to have received ≥ 2, but not more than 9, injections with any anti-VEGF agent in the study eye. To meet anti-VEGF responsiveness criteria, the study eye must either have demonstrated a documented decrease in central foveal thickness (CFT) of 50 µm or stable or improved BCVA following intravitreal anti-VEGF treatment initiation. Prescreening with run-in intravitreal ranibizumab treatment was available to eligible patients to determine eligibility. All nAMD choroidal neovascularization (CNV) lesion subtypes were permitted and patients were required to have Snellen equivalent BCVA of 20/20–20/200 using Early Treatment Diabetic Retinopathy Study (ETDRS) charts. Diagnosis of nAMD and CNV features were confirmed at screening by a central reading center. Investigators confirmed anti-VEGF responsiveness and all other inclusion and exclusion criteria. Key ocular exclusion criteria were subfoveal fibrosis, atrophy, or large submacular hemorrhage in the study eye. Treatment with oral anticoagulants or antiplatelets other than aspirin was also exclusionary for the main Ladder trial.

Randomization, Intervention, and Masking

Patients were randomly assigned 3:3:3:2 to treatment with the PDS filled with ranibizumab 10 mg/mL, 40 mg/mL, or 100 mg/mL formulations or to treatment with monthly intravitreal ranibizumab 0.5 mg injections (Lucentis®, Genentech, Inc., South San Francisco, CA). For PDS patients, implant refills were performed on a pro re nata basis according to predefined criteria. Trial duration was up to ~38 months. Randomization was performed by interactive voice/web response system and stratified based on BCVA score (≤ 65 ETDRS letters vs. ≥ 66 ETDRS letters) and number of prior intravitreal anti-VEGF injections (≤ 3 injections vs. ≥ 4 injections). Visual acuity assessors were masked to both the patient study eye and patient

treatment. Within the PDS treatment arms, patients and all study site personnel were masked to ranibizumab formulation assignment. Patients and other study site personnel were not masked regarding patient assignment to either PDS treatment or monthly intravitreal ranibizumab 0.5 mg injections.

Study Treatments and Assessments

Port Delivery System with Ranibizumab Implant

The PDS consists of a surgically implanted, refillable intraocular implant (Fig 1) designed for the continuous delivery of a customized formulation of ranibizumab, as well as ancillary devices for the surgical, initial fill, and in-office refill procedures. In Ladder, the PDS was tested with 3 customized ranibizumab formulations (10 mg/mL, 40 mg/mL, and 100 mg/mL).

Port Delivery System with Ranibizumab Implant Insertion and Removal Surgery

Implant insertion was performed in an operating room under local anesthesia, using standard sterile aseptic surgical techniques. After conjunctival peritomy in the superotemporal quadrant, a stab incision at the pars plana was performed 4 mm posterior to the limbus (original surgical technique); alternatively, a scleral dissection followed by ablation of the exposed pars plana with 532-nm laser with additional diathermy as required was performed (optimized surgical technique, implemented in the May 2016 Instructions for Use procedure update). The implant, filled in the operating room with 1 of the 3 ranibizumab formulations, was then inserted in the scleral wound using the PDS insertion tool, followed by careful suturing of conjunctiva and Tenon's capsule to provide good coverage of the implant flange (Video S1, available at www.aaojournal.org). When required by the protocol, implant removal was performed using the customized PDS explant tool. The procedure was performed in an operating room using standard sterile aseptic techniques and local anesthesia.

Port Delivery System with Ranibizumab Implant Refill Procedure

When required, implant refill procedures were performed in office as part of the monthly study visit. Briefly, using standard aseptic techniques and local anesthesia, the PDS refill needle was inserted perpendicularly through the conjunctiva and the center of the underlying implant septum. For each refill, 0.1 mL of the specified ranibizumab formulation was injected into the implant using a dual lumen refill needle that simultaneously withdraws the preexisting ranibizumab solution remaining in the implant, ensuring total fluid exchange of old drug with new drug in the reservoir (Video S2, available at www.aaojournal.org).

Port Delivery System with Ranibizumab Implant Refill Criteria

All PDS patients were assessed at each monthly visit and implant refills were performed if any of the following occurred due to nAMD disease activity: 1) increase in CFT ≥ 75 µm on spectral domain optical coherence tomography (SD-OCT) at the current visit compared with the average CFT over the last 2 available measurements, 2) increase in CFT of ≥ 100 µm from the lowest CFT measurement on study, 3) decrease of ≥ 5 letters in BCVA at the current visit compared with the average BCVA over the last 2 available measurements, 4) decrease of ≥ 10 letters from best recorded BCVA on study, or 5) presence of new macular hemorrhage. Best-corrected visual acuity and CFT criteria were slightly modified during the trial; see Appendix S3, available at www.aaojournal.org, for a full description of modifications.

Port Delivery System with Ranibizumab Rescue Criteria and Treatment

Open-label intravitreal ranibizumab 0.5 mg injections were available to all PDS patients 1–2 months after vitreous hemorrhage associated with BCVA loss, if neither assessment of the macula nor SD-OCT could be performed, if lack of clinical efficacy criteria were met, or in case of progressive worsening of BCVA and/or CFT over 2 consecutive visits due to nAMD disease activity that did not hit thresholds to trigger a refill (discussion with medical monitor necessary). Lack of clinical efficacy was defined as: 1) BCVA loss of ≥ 15 letters from best

recorded BCVA following 2 consecutive implant refills occurring 1 month apart due to nAMD disease activity unless there was ≥ 5-letter increase in BCVA that would trigger an implant refill, or 2) an increase in CFT of ≥ 150 µm from lowest recorded CFT measurement following 2 consecutive implant refills occurring 1 month apart unless there was a decrease in CFT ≥ 75 µm from last refill that would trigger implant refill (Appendix S3).

When the trial started, implant removal was mandated if lack of clinical efficacy criteria were met. Subsequent internal assessment of 8 explanted implants determined that lack of clinical efficacy was not associated with inadequate implant performance or implant clogging. The trial protocol was then amended so patients meeting lack of clinical efficacy criteria could keep the implant in the eye, receive a rescue open-label intravitreal ranibizumab 0.5 mg injection, and undergo a mandatory implant refill with the 100 mg/mL formulation at the next monthly visit. At all subsequent visits, patients were assessed for implant refill criteria, and if criteria were met, implant refill was performed with the ranibizumab 100 mg/mL formulation (Appendix S3).

Monthly Intravitreal Ranibizumab 0.5 mg Injections

In the control arm, patients received intravitreal ranibizumab 0.5 mg injections (50 µL of the 10 mg/mL US Food and Drug Administration–approved formulation) at day 1 and then at each monthly visit through trial completion.

Assessments

Standard safety and ocular assessments, including BCVA and CFT, were performed at each monthly visit. In the PDS treatment arms, additional safety and functional outcomes were assessed at days 2, 7, and 14 to monitor the implant insertion procedure; additional safety assessments were also performed 7 days after each implant refill.

Outcomes

The prespecified primary efficacy endpoint was the time to first implant refill assessed when the last enrolled patient completed the month 9 visit. Secondary efficacy outcomes included change in visual function and changes in CFT, as assessed by the central reading center. Central foveal thickness measurements were conducted using 2 methods. The prespecified measurement was performed from the inner limiting membrane to Bruch's membrane. The second, additional measurement, was performed from the inner limiting membrane to the retinal pigment epithelium, excluding pigment epithelial detachment (PED) height. Explanted implants were visually inspected to assess implant integrity and in vitro drug release evaluations were performed to assess implant functionality. In addition, samples were collected for serum pharmacokinetics and antidrug antibody (ADA) assessment. Safety outcomes were assessed through a summary of ocular and nonocular adverse events (AEs) and incidence of ADA. Prespecified PDS-associated AEs were also assessed.

Data Analysis and Statistical Methods

An estimated trial sample size of 220 randomized patients was determined to be adequate to meet the primary objective of evaluating the relative efficacy of the ranibizumab 10 mg/mL, 40 mg/mL, and 100 mg/mL formulations as assessed by time to first implant refill. A sample size of ~60 patients in each PDS treatment arm provided 80% power to detect a hazard ratio (HR) of 0.66 in time to first implant refill between the PDS 10 mg/mL and PDS 100 mg/mL treatment arms using a log-rank test at a 1-sided significance level of 15% assuming 85 events occurred at the time of primary analysis.

Efficacy outcomes were evaluated in the modified intent-to-treat population comprised of patients who were randomized to a study treatment arm and received ≥ 1 study treatment. The safety-evaluable population comprised all patients who received ≥ 1 dose of study drug according to the assigned treatment. Time to first implant refill analysis was conducted using

observed data. The censoring date was defined as the date of a patient's last visit before the cutoff date or the date when the patient discontinued from the study, whichever occurred first. Time to first implant refill was also censored for the following patients: 1) at the time of an intravitreal anti-VEGF injection in study eye if administered before the first required refill; 2) at the time the refill criteria could not be assessed, defined as when ≥ 2 refill variables (BCVA, CFT, or new macular hemorrhage) could not be evaluated for any reason, or were affected by a clinical reason different from nAMD activity, before the first required refill; and 3) at the time of implant explantation. Both unstratified and stratified log-rank tests were used to estimate the pairwise HR and its 70% confidence interval (CI) among the 3 PDS treatment arms. For the stratified log-rank test with a 1-sided significance level of 15%, the stratification factors were baseline BCVA score (≤ 65 ETDRS letters vs. ≥ 66 ETDRS letters) and number of intravitreal anti-VEGF injections before baseline (≤ 3 injections vs. ≥ 4 injections). The Kaplan-Meier approach was used to estimate median time to first implant refill and the 6-month percentages of patients without any refill for each treatment group.

A mixed-effect model repeated measures (MMRM) analysis was used to generate adjusted mean BCVA change from baseline values that accounted for baseline differences across the treatment arms. The MMRM analysis used change from baseline in BCVA as the response and included terms for treatment group, visit, treatment-by-visit, interaction, baseline BCVA score (continuous), baseline BCVA (≤ 65 ETDRS letters vs. ≥ 66 ETDRS letters), and number of intravitreal anti-VEGF injections before baseline (≤ 3 injections vs. ≥ 4 injections). An unstructured covariance structure was used, and assessment was censored for PDS patients at the time of an intravitreal anti-VEGF injection in the study eye if administered before month 9 and at the time of implant explant. Observed, descriptive data were used to assess mean BCVA change over time comparing the early treatment response in all patients versus patients enrolled after implementation of the optimized surgical

procedure on May 2016. The same MMRM analysis method for BCVA outcomes was used to assess adjusted mean CFT change from baseline. Descriptive summaries were used for all secondary endpoints for preliminary assessments of differences between each of the PDS arms and the monthly intravitreal treatment arm.

Oral Antithrombotic Substudy

A nonrandomized, uncontrolled, open-label exploratory substudy assessing the safety, efficacy, and pharmacokinetics of the PDS filled with ranibizumab 100 mg/mL in patients with nAMD who required ongoing oral antithrombotic therapy was conducted as part of the Ladder trial. The substudy was initiated at selected sites (Appendix S1) after Ladder enrollment was complete and enrolled a separate trial population of 11 patients who were on oral antithrombotic therapy for a preexisting medical condition. The primary endpoint of the substudy was the rate of vitreous hemorrhage secondary to choroidal bleeding that did not spontaneously resolve by the month 1 visit after implant insertion surgery. Oral antithrombotic substudy patients were evaluated separately and were not included in any of the main Ladder analyses.

Results

Patient Disposition

A total of 232 patients with nAMD were randomized 3:3:3:2 to 1 of 4 treatment arms: 1) PDS ranibizumab 10 mg/mL, 2) PDS ranibizumab 40 mg/mL, 3) PDS ranibizumab 100 mg/mL, or 4) monthly intravitreal ranibizumab 0.5 mg injections. The first patient was enrolled on September 29, 2015, and the last patient was enrolled on September 5, 2017. The data from 7 patients were unusable due to a breach of Good Clinical Practice at 1 study site and another 5 randomized patients were never treated, resulting in a modified intent-to-treat population of 220 patients with 58, 62, 59, and 41 patients in the PDS 10 mg/mL, 40 mg/mL,

100 mg/mL, and monthly intravitreal ranibizumab 0.5 mg injection arms, respectively (Fig S1, available at www.aaojournal.org). For the primary analysis, the modified intent-to-treat and safety populations were identical (N = 220). At the time of the primary analysis, the percentages of patients that withdrew from the study or discontinued treatment in the study eye were comparable across treatment arms (Fig S1). Of the 220 patients in the modified intent-to-treat population, 11 (5.0%) discontinued the study and 18 (8.2%) discontinued treatment in the study eye.

Demographics and Baseline Characteristics of the Study Population

Baseline demographic and ocular characteristics are summarized in Table 1. Overall patient demographics were well balanced across treatment arms. Ocular characteristics were generally well balanced across arms, with a slight imbalance in CFT with increased baseline values in 2 of the PDS arms. The imbalance was minimized when PED height was excluded. Also of note was the generally good baseline vision across arms, with two-thirds of all patients having 20/40 or better vision at baseline. In the overall population, the mean number of anti-VEGF injections before baseline was 2.9.

Primary Efficacy Outcome

The prespecified primary outcome measure was the time to first implant refill assessed when the last patient enrolled completed the month 9 visit, at which point the mean (range) time on study was 16.8 (9.8–33.0) months for all PDS patients. A Kaplan-Meier survival analysis was used to compare rates at which first implant refills occurred in each PDS treatment arm (Fig 2A). The median time to first implant refill was 8.7, 13.0, and 15.0 months in the PDS 10 mg/mL, 40 mg/mL, and 100 mg/mL arms, respectively. The percentage of patients who did not require an implant refill for ≥ 6 months was 63.5%, 71.3%, and 79.8% in the PDS 10 mg/mL, 40 mg/mL, and 100 mg/mL arms, respectively (Fig 2B). In a stratified analysis that adjusted for baseline BCVA and number of prior anti-VEGF injections, the median time to first

implant refill was significantly longer in the PDS 100 mg/mL arm than the PDS 10 mg/mL arm (15.0 vs. 8.7 months, respectively; HR, 0.50 [70% CI, 0.38–0.66]; *P* = 0.0066) and for the PDS 40 mg/mL arm versus the PDS 10 mg/mL arm (median, 13.0 vs. 8.7 months, respectively; HR, 0.60 [70% CI, 0.46–0.78]; *P* = 0.0415; Table 2). Although the PDS 100 mg/mL arm trended towards a longer median time to first implant refill, there was no significant difference compared with the PDS 40 mg/mL arm (15.0 vs. 13.0 months, respectively; HR, 0.7523 [70% CI, 0.69–1.22]; *P* = 0.7523). Results of an unstratified analysis were consistent with those of the stratified analysis.

Secondary Efficacy Outcomes

Vision Outcomes

Because patients were previously treated and anti-VEGF responsive with good baseline BCVA, the treatment arms were assessed for their ability to maintain baseline vision. A dose response was observed across the PDS arms. At month 9, the adjusted mean BCVA change from baseline in the PDS 10 mg/mL, 40 mg/mL, and 100 mg/mL arms was –3.2, –0.5, and +5.0 ETDRS letters, respectively. At month 9, the mean adjusted BCVA change from baseline was +3.9 ETDRS letters in the monthly intravitreal ranibizumab 0.5 mg injection arm (Fig 3). At month 9, there was a +1.1 (95% CI, –2.4, +4.7) ETDRS letter difference between the PDS 100 mg/mL and monthly intravitreal ranibizumab 0.5 mg injection arms. Neither a noninferiority (NI) test nor a NI margin were prespecified in Ladder. In a post hoc analysis assuming a 4.5 ETDRS letter NI margin, the NI test was met between the PDS 100 mg/mL and monthly intravitreal ranibizumab 0.5 mg injection treatment arms at month 9 (lower bound of the 95% CI in the difference calculation was larger than 4.5 ETDRS letters). These results indicate that vision outcomes in the PDS 100 mg/mL arm were comparable with that of the monthly intravitreal ranibizumab 0.5 mg injection treatment arm.

Observed data (Fig S2, available at www.aaojournal.org) were comparable with the MMRM analysis shown in Figure 3 and a dose response was also observed across the PDS arms for the percentage of patients with a mean BCVA improvement from baseline of ≥ 5 or ≥ 10 ETDRS letters at month 9 (Table S1, available at www.aaojournal.org). In the PDS arms, there was a temporary and reversible postinsertion surgery drop in vision that was expected after vitreoretinal surgery. In the overall population, vision generally returned to baseline by month 2; in PDS patients who were implanted after the May 2016 procedure update, the drop in BCVA from baseline was reduced in magnitude and vision generally returned to baseline by month 1 (Fig S3, available at www.aaojournal.org).

Anatomic Outcomes

Similar to vision outcomes, as Ladder patients were previously treated with and responsive to anti-VEGF therapy, patients were assessed for their ability to maintain baseline CFT (Fig 4). As with baseline values, variability in CFT change from baseline across arms was generally reduced when subfoveal PED height was excluded. At month 9, adjusted mean CFT change from baseline excluding PED height was +54.4 µm, –0.5 µm, –1.7 µm, and –6.3 µm in the PDS 10 mg/mL, 40 mg/mL, and 100 mg/mL and monthly intravitreal ranibizumab 0.5 mg injection treatment arms, respectively. At month 9, adjusted mean CFT change from baseline including PED height was +57.4 µm, 22.2 µm, 11.1 µm, and –29.3 µm in the PDS 10 mg/mL, 40 mg/mL, and 100 mg/mL and monthly intravitreal ranibizumab 0.5 mg injection treatment arms, respectively (Fig 4). Observed data (Fig S4, available at www.aaojournal.org) were similar to the MMRM analysis shown in Figure 4.

Implant Functionality and Drug Exposure

In the early part of the trial, patients who experienced progressive nAMD disease worsening that met lack of clinical efficacy criteria underwent surgical removal of the PDS implant to evaluate implant functionality. At the time of the primary analysis, 12 PDS implants had been

explanted: 6 due to lack of clinical efficacy, 4 due to an AE, and 2 due to physician's decision. The time of explant ranged from day 8 to day 500 following implant insertion, with a median time of explanation of 274 days. Measurable levels of ranibizumab were present in serum at the time of implant removal, suggesting that drug was still being released from the reservoir into the eye and exiting the eye into the systemic circulation. In vitro testing of 8 explanted implants confirmed that all implants had appropriate release of ranibizumab with no evidence of clogging. Because implant functionality was not a cause for lack of clinical efficacy, the protocol was amended to allow PDS patients who met the lack of clinical efficacy criteria to keep the implant in the eye with a modified treatment protocol (see Methods and Appendix S3).

At the time of the primary analysis, the mean time on study was 16.8 months for patients in the PDS treatment arms and 16.4 months for patients in the monthly intravitreal ranibizumab 0.5 mg injection arm (Table 3). The mean total number of ranibizumab treatments was 3.7, 2.6, and 2.4 in the PDS 10 mg/mL, 40 mg/mL, and 100 mg/mL treatment arms, respectively. In contrast, the total number of ranibizumab treatments was 16.8 in patients in the monthly intravitreal ranibizumab 0.5 mg injection treatment arm. In total, 22.4%, 4.8%, and 1.7% of patients in the PDS 10 mg/mL, 40 mg/mL, and 100 mg/mL treatment arms, respectively, met lack of clinical efficacy criteria. In the PDS 10 mg/mL and 40 mg/mL treatment arms, the majority of patients (11/16) who met lack of clinical efficacy criteria kept the PDS implant and were managed with rescue intravitreal ranibizumab treatment and implant refills with the ranibizumab 100 mg/mL formulation.

Safety

As expected given the surgical nature of the study, more ocular AEs were observed in the PDS arms than in the monthly intravitreal ranibizumab 0.5 mg injection arm, particularly during the perioperative period (Table S2, available at www.aaojournal.org). No ocular

serious AEs (SAEs) were reported in the monthly intravitreal ranibizumab 0.5 mg injection treatment arm. Ocular SAEs were reported in 16 of 179 (8.9%) PDS-treated patients. The most frequent SAE was vitreous hemorrhage, occurring in 7 (3.9%) patients in the overall PDS-treated population.

Table 4 shows all PDS-associated AEs in the safety-evaluable population. The majority of AEs occurred within 1 month of PDS implant insertion. At study outset, vitreous hemorrhage occurred in 11 of the first 22 (50.0%) PDS-treated patients. Following implementation of the optimized implant insertion procedure in May 2016 that incorporated pars plana laser ablation, vitreous hemorrhage occurred in 7 of 157 (4.5%) PDS-treated patients, of which 1 event was classified as serious. Endophthalmitis occurred in 3 PDS patients, 1 in each treatment arm. In terms of timing, 1 endophthalmitis event occurred a few days after PDS implant insertion. The other 2 events occurred months after PDS implant insertion, with 1 event being preceded by conjunctival retraction that was not promptly repaired due to patient noncompliance; the second late event was not associated with any proximate intervention or conjunctival defect. For all 3 patients, cultures were negative, the PDS implant was explanted, and, after resolution, BCVA returned to baseline. Four rhegmatogenous retinal detachments occurred in PDS-treated patients. One event occurred soon after PDS implant insertion, while the remaining 3 occurred later in the trial. The implant was retained in 2 patients in whom the retinal detachment was repaired by pneumatic retinopexy or vitrectomy and was explanted in 2 patients in whom the detachment was repaired by scleral buckle.

In general, the systemic safety profile of PDS treatment was comparable with monthly intravitreal ranibizumab 0.5 mg injection treatment (Table S3, available at www.aaojournal.org). There was, however, a higher rate of a few System Organ Class events in the PDS treatment arms compared with the monthly intravitreal ranibizumab 0.5 mg arm.

These included gastrointestinal AEs; injury, poisoning, and procedural complications; and nervous system disorders. The majority of gastrointestinal disorder events were nonserious, with nausea, constipation, and gastroesophageal reflux disease being the most common events (> 2 patients; Table S4, available at www.aaojournal.org). The events were mild and moderate in severity and resolved quickly. The majority of procedural complication events were nonserious and included fractures, sprains, and dislocations that had no temporal relationship with PDS implant insertion or refill procedures. The majority of nervous system disorders were nonserious events such as headache that occurred in the postoperative period and were associated with postoperative pain and discomfort from conjunctival sutures (19/25 [76.0%] events). Eighteen of 19 headache events in the postoperative period resolved within 1 month.

Additional Assessments

In terms of pharmacokinetics, in vitro studies have shown that ranibizumab release from the PDS is a function of concentration in the reservoir and decays exponentially over time, following Fick's law.[21] In the current study, active ranibizumab was measurable (with a lower limit of quantification of 15 pg/mL)[22] in serum for ≥ 15 months after insertion of the PDS implant filled with ranibizumab 100 mg/mL, as would be expected based on the in vitro studies. Antidrug antibody development was also assessed (Table S5, available at www.aaojournal.org). Because all Ladder patients were previously treated with ranibizumab, ADA status at time of study entry may reflect response to previous ranibizumab treatment in the study or fellow eye, rather than treatment-naïve prevalence. Overall, at the time of the primary analysis, the percentages of patients in each arm who were ADA positive at time of study entry (0–10.5%) or developed treatment-emergent ADAs during the course of the study (3.5–13.6%) were within the range observed in previous clinical trials with ranibizumab administered via intravitreal injection.[3,7,23]

Oral Antithrombotic Agent Substudy

Patients on an oral antithrombotic agent were prohibited from enrolling in the main Ladder trial, resulting in the exclusion of a large number of otherwise eligible patients. Once it was determined that laser ablation of the pars plana before incision markedly reduced the incidence and severity of vitreous hemorrhage after PDS implant insertion, a substudy was initiated in a limited number of study sites to determine the safety of the optimized implant insertion procedure in patients on oral anticoagulants. Eleven patients with nAMD on oral antithrombotic therapy were recruited and received the PDS implant with the ranibizumab 100 mg/mL formulation. Interruption of the antithrombotic agent before PDS implant insertion was left to the discretion of the investigator after consultation with the prescribing physician to assess the risk based on the needs of each patient and the antithrombotic agent in question. Anticoagulant treatment was briefly interrupted in 3 of 4 patients on warfarin sodium (Coumadin®, Bristol-Myers Squibb Company, Princeton, NJ), 4 of 5 patients on apixaban (Eliquis®, Bristol-Myers Squibb Company), and 2 of 2 patients on dabigatran etexilate mesylate (Pradaxa®, Boehringer Ingelheim Pharmaceuticals, Inc., Ridgefield, CT). In the 9 patients whose anticoagulant treatment was interrupted, the mean duration of interruption was 3 days (range, 2–5 days). No patients experienced vitreous hemorrhage after PDS implant insertion with the optimized surgical technique, with a minimum follow-up of 2 months.

Discussion

The phase 2 Ladder trial met its primary objective and successfully assessed the relative efficacy of PDS treatment with ranibizumab 10 mg/mL, 40 mg/mL, and 100 mg/mL formulations. For primary and secondary vision endpoints, a dose response was observed across the PDS treatment arms, with patients in the PDS 100 mg/mL treatment arm

experiencing the greatest clinical benefit. In addition, a dose response was seen in the percentage of patients not receiving any refill at month 6 and other refill-related endpoints. Results for the PDS 100 mg/mL were the most promising, with a median time to first implant refill of 15.0 months and 79.8% of patients who went ≥ 6 months without meeting implant refill criteria. PDS treatment also successfully reduced the overall treatment burden for patients, with PDS patients receiving ~80% fewer ranibizumab treatments than patients in the monthly intravitreal ranibizumab 0.5 mg injection treatment arm at the time of the primary analysis. Importantly, vision and anatomic outcomes at month 9 were comparable between patients in the PDS 100 mg/mL arm and patients in the monthly intravitreal ranibizumab 0.5 mg injection treatment arm, indicating that clinical efficacy need not be sacrificed to reduce treatment burden. Taken together, these results suggest that the PDS is a good candidate to change the treatment paradigm in nAMD and respond to the current unmet need to reduce treatment burden while maintaining or improving patient outcomes.

While the optimized PDS implant insertion surgery and in-office refill procedure were generally well tolerated, the Ladder trial also provided a number of valuable technical insights into the best surgical methods for PDS implant insertion. The high rate of vitreous hemorrhage following PDS implant insertion early in the trial (11/22 patients [50%]) led to enrollment being temporarily paused. This allowed for a preclinical surgical study to be conducted as part of a comprehensive analysis to determine the root cause of the vitreous hemorrhage. Based on the study results that identified the pars plana at the incision site as the main source of bleeding,[24] an optimized surgical procedure that included laser ablation of the pars plana at the incision site was implemented in the study when enrollment restarted. Following the introduction of the optimized surgical procedure, the incidence of postoperative vitreous hemorrhage decreased to less than 5% (7/157 patients).

The reduction in the incidence of vitreous hemorrhage after optimization of the implant insertion procedure raised the question of whether patients on an oral antithrombotic therapy could safely undergo PDS implant insertion. This is an important question, because ~25% of patients with nAMD are on an oral antithrombotic therapy.[21] A small substudy of 11 patients with nAMD receiving concurrent treatment with different antithrombotic agents helped to address this question. While the substudy was not powered to assess meaningful differences between patients who did and did not interrupt oral antithrombotic treatment, it did generate useful information regarding whether laser ablation of the pars plana was sufficient to mitigate the risk of vitreous hemorrhage in this patient population, which has a higher risk of bleeding. As none of the patients experienced vitreous hemorrhage after PDS implant insertion, the results suggest there is a low risk of vitreous hemorrhage for patients with nAMD on anticoagulants who undergo the optimized PDS implant insertion procedure.

Additional clinically relevant AEs related to the PDS implant insertion procedure, including endophthalmitis, rhegmatogenous retinal detachment, retinal tears, and conjunctival erosion or retraction were reported in PDS patients. These events were managed accordingly and did not result in severe vision loss. Overall, postsurgical AEs in PDS-treated patients were consistent with what would be expected for similar surgical procedures. Videos of each implant insertion procedure were analyzed to identify areas for improvement of the surgical procedure to minimize the risk of procedure-related AEs. Rigorous surgical training has been instituted with the aim to help further mitigate the risk of AEs as the PDS continues to be developed and studied.

As an indwelling nonbiodegradable implant, the PDS is one of a number of strategies being tested in clinical trials aimed at achieving sustained intravitreal suppression of VEGF. Other strategies include surgically inserted or injectable biodegradable polymer implants and drug encapsulation in injectable liposomes, microparticles, or nanoparticles. Various forms of

gene therapy using different vectors are also being explored.[25,26] The PDS is the first system, however, that has provided the opportunity to investigate the biologic response to sustained intravitreal suppression of VEGF in patients with nAMD. The extended median time to first implant refill and the maintenance of vision in PDS-treated patients indicate the clinical efficacy of sustained VEGF suppression. These results raise the question of whether sustained intravitreal VEGF suppression mediated by continuous ranibizumab delivery is capable of better controlling the nAMD disease process compared with pulsatile intravitreal treatment. Another important open question is whether patients with nAMD who need more frequent anti-VEGF treatment can be preidentified; however, biomarkers for treatment response have not been found at this time. Further studies are needed to address these important issues. Additional imaging analyses and long-term data from the ongoing Portal extension study (NCT03683251) may shed light on these compelling questions.

The heterogeneous response of patients with nAMD to bolus intravitreal injections is one of the more challenging aspects of nAMD management. While the idea of individualizing treatment by identifying the optimal interval between injections to prevent recurrences is appealing, disease activity can vary over time in the same patient, allowing occasional disease reactivation and associated vision loss. With 79.8% of patients in the PDS 100 mg/mL arm going ≥ 6 months before requiring an implant refill, the data suggest that PDS treatment may introduce disease control predictability to the management of what has to date been an unpredictable disease. Furthermore, pharmacokinetic analysis indicates that the patients who met implant refill criteria before month 6 were still having ranibizumab released into the eye. Taken together, these results indicate that with the PDS, it may be feasible to use a fixed multimonth refill schedule to reduce treatment burden without sacrificing efficacy in patients with nAMD.

A limitation of this study is the unavoidable variability that occurs in any clinical trial that has a surgical component. A number of steps were taken to reduce, manage, and learn from this variability, including surgical training aimed to standardize the surgical procedure across investigators, support from well-trained study team members during PDS implant insertion and refill procedures, and video recording for documentation, review, and study. This provided important learnings that contributed to the optimization of the implant insertion and refill procedures and shaped the investigator training plan for future studies. While the procedural and protocol amendments throughout the course of the study would be considered a weakness of a pivotal study, they allowed this phase 2 trial to efficiently evaluate a novel method for continuous delivery with a surgical component for the first time on a large scale. Initial learnings in Ladder led to the optimization of study methods and procedures that will help to enhance the safety and efficacy for future trials. Another limitation is that Ladder enrolled patients who were responsive to anti-VEGF treatment and were diagnosed with nAMD in the study eye within 9 months from the screening visit; therefore, the results may not be generalizable to patients with a longstanding nAMD diagnosis who have been receiving anti-VEGF treatment for years. Further studies will be needed to assess the usefulness of the PDS in different nAMD populations.

In conclusion, the phase 2 Ladder trial of the PDS evaluated the efficacy and safety of continuous intraocular delivery of an anti-VEGF biologic in patients with nAMD. Continuous intravitreal delivery of ranibizumab through the PDS implant resulted in sustained suppression of VEGF activity sufficient to confer clinical efficacy without the need for monthly intravitreal injections in the majority of patients. The results demonstrate that sustained VEGF inhibition for months at a time is possible, and that visual and anatomic results comparable with monthly intravitreal injection can be achieved with a substantial reduction in the treatment burden. Finally, the Ladder results provide proof of concept that biologics or small

molecules can be safely delivered to the eye for months at a time through a permanent refillable intraocular reservoir. The results from the phase 2 Ladder trial provide a glimpse of how treatments for nAMD and other retinal vascular diseases, including diabetic eye disease and retinal vein occlusion, may evolve in the future. The next step in this evolution of PDS for nAMD is the pivotal Archway phase 3 trial (ClinicalTrials.gov NCT03677934).

Data Sharing Statement

Qualified researchers may request access to individual patient level data through the clinical study data request platform (www.clinicalstudydatarequest.com). Further details on Roche's criteria for eligible studies are available here (https://clinicalstudydatarequest.com/Study-Sponsors/Study-Sponsors-Roche.aspx). For further details on Roche's Global Policy on the Sharing of Clinical Information and how to request access to related clinical study documents, see here (https://www.roche.com/research_and_development/who_we_are_how_we_work/clinical_trials/our_commitment_to_data_sharing.htm).

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Figure legends

Figure 1. Port Delivery System with ranibizumab (PDS) implant. **A**, PDS implant showing 4 key components: the extrascleral flange that anchors the implant in the sclera, the self-sealing septum that allows for implant refills, the implant body that contains the drug reservoir for the ranibizumab formulation, and the release control element that controls the rate of ranibizumab diffusion from the implant into the vitreous. Patient images from a PDS-implanted patient with (**B**) eye in primary position (implant not visible), (**C**) eye looking up with implant visible through dilated pupil, and (**D**) eye looking down to visualize PDS septum.

Figure 2. Time to first implant refill, modified intent-to-treat population. **A**, Data are included for all Port Delivery System with ranibizumab (PDS) patients through month 9 and for all study visits completed after month 9 (data collection ongoing). Patient data censored when last visits were before cutoff date or if they discontinued the study, whichever occurred first. Time to first implant refill censored at the time of intravitreal injection, at the time refill criteria could not be assessed, and at the time of explant before the first refill. **B**, Bars show the percentage of patients in each PDS arm that did not meet refill criteria through month 6.

Figure 3. Adjusted mean best-corrected visual acuity (BCVA) change from baseline, modified intent-to-treat population. All patients were previously treated with and responsive to anti–vascular endothelial growth factor (VEGF) therapy. The mixed-effect model repeated measures analysis used change from baseline BCVA as the response and included terms for treatment group, visit, treatment-by-visit, interaction, baseline BCVA score (continuous), baseline BCVA (≤ 65 Early Treatment Diabetic Retinopathy Study [ETDRS] letter score vs. ≥ 66 ETDRS letter score), and number of intravitreal anti-VEGF injections before baseline (≤ 3

721 injections vs. ≥ 4 injections). An unstructured covariance structure was used; assessment
722 was censored for PDS patients at the time of an intravitreal anti-VEGF injection in the study
723 eye if administered before month 9 and at the time of PDS removal. Data from 13, 2, and 4
724 patients in the PDS 10 mg/mL, 40 mg/mL, and 100 mg/mL arms were censored before month
725 9, respectively. The vertical bars represent 95% confidence intervals.
726
727 **Figure 4**. Adjusted mean central foveal thickness (CFT) change from baseline, modified
728 intent-to-treat population. All patients were previously treated with and responsive to anti–
729 vascular endothelial growth factor (VEGF) therapy. The mixed-effect model repeated
730 measures analysis used change from baseline CFT as the response and included terms for
731 treatment group, visit, treatment-by-visit, interaction, baseline CFT value (continuous),
732 baseline best-corrected visual acuity (≤ 65 Early Treatment Diabetic Retinopathy Study
733 [ETDRS] letter score vs. ≥ 66 ETDRS letter score), and number of intravitreal anti-VEGF
734 injections before baseline (≤ 3 injections vs. ≥ 4 injections). An unstructured covariance
735 structure was used; assessment was censored for Port Delivery System with ranibizumab
736 (PDS) patients at the time of an intravitreal anti-VEGF injection in the study eye if
737 administered before month 9 and at the time of PDS removal. The points show the adjusted
738 mean change from baseline CFT (**A**) excluding subfoveal pigment epithelial detachment
739 (PED) height or (**B**) including PED height. Data from 13, 2, and 4 patients in the PDS 10
740 mg/mL, 40 mg/mL, and 100 mg/mL arms were censored before month 9, respectively.
741 Vertical bars represent 95% confidence intervals. ILM = inner limiting membrane; RPE =
742 retinal pigment epithelium.

Online Only Supplemental Materials

1 Table 1. Demographic and Baseline Characteristics of Ladder Participants, Modified Intent-to-Treat Population

	PDS Ranibizumab 10 mg/mL (n = 58)	**PDS Ranibizumab 40 mg/mL (n = 62)**	**PDS Ranibizumab 100 mg/mL (n = 59)**	**Monthly Intravitreal Ranibizumab 0.5 mg (n = 41)**	**All Patients (N = 220)**
Demographics					
Age (yrs)					
Mean (SD)	74.3 (8.3)	74.9 (8.4)	73.4 (8.0)	71.8 (8.8)	73.8 (8.4)
Range	56–92	50–90	57–91	52–85	50–92
Sex, n (%)					
Male	22 (37.9%)	23 (37.1%)	21 (35.6%)	13 (31.7%)	79 (35.9%)
Race, n (%)					
White	57 (98.3%)	61 (98.4%)	56 (94.9%)	41 (100.0%)	215 (97.7%)
Asian	0	0	2 (3.4%)	0	2 (0.9%)
American Indian or Alaska Native	0	0	1 (1.7%)	0	1 (0.5%)
Black or African American	1 (1.7%)	0	0	0	1 (0.5%)
Not available	0	1 (1.6%)	0	0	1 (0.5%)
Ethnicity, n (%)					
Not Hispanic or Latino	55 (94.8%)	56 (90.3%)	57 (96.6%)	39 (95.1%)	207 (94.1%)
Hispanic or Latino	3 (5.2%)	3 (4.8%)	2 (3.4%)	1 (2.4%)	9 (4.1%)
Not available	0	3 (4.8%)	0	1 (2.4%)	4 (1.8%)
Study eye baseline characteristics					
BCVA (ETDRS letter score)					
Mean (SD) Approximate Snellen equivalent	69.3 (12.8) 20/40	69.9 (11.7) 20/40	70.4 (9.8) 20/40	70.6 (12.7) 20/40	70.0 (11.7) 20/40
Median	72.5	71.5	72.0	73.0	72.0

Range	34–87	34–88	37–85	34–88	32–88
BCVA (approximate Snellen equivalent), n (%)					
20/200 or worse	2 (3.4%)	2 (3.2%)	1 (1.7%)	2 (4.9%)	7 (3.2%)
Better than 20/200 to worse than 20/40	17 (29.3%)	19 (30.6%)	20 (33.9%)	12 (29.3%)	68 (30.9%)
20/40 or better	39 (67.2%)	41 (66.1%)	38 (64.4%)	27 (65.9%)	145 (65.9%)
Lens status, n (%)					
Phakic	31 (53.4%)	26 (41.9%)	28 (47.5%)	26 (63.4%)	111 (50.5%)
Pseudophakic	27 (46.6%)	36 (58.1%)	31 (52.5%)	15 (36.6%)	109 (49.5%)
Anti-VEGF treatment-naïve patients who completed run-in, n (%)	23 (39.7%)	30 (48.4%)	23 (39.0%)	12 (29.3%)	88 (40.0%)
No. of prior anti-VEGF injections					
Mean (SD)	2.7 (1.2)	2.8 (1.2)	3.1 (1.5)	2.9 (1.3)	2.9 (1.3)
Median	2.0	2.0	3.0	2.0	2.0
Range	2–7	2–6	2–8	2–7	2–8
Baseline CFT (µm)					
CFT ILM-Bruch's, including PED height, mean (SD)	306.8 (131.6)	297.3 (127.3)	274.7 (110.2)	280.1 (118.1)	290.0 (122.4)
CFT ILM-RPE, excluding PED height, mean (SD)	194.4 (72.6)	181.8 (73.2)	183.1 (69.2)	185.0 (61.6)	186.1 (69.6)
Baseline RPE + PED thickness (µm)					
Mean (SD)	107.6 (118.6)	110.1 (111.4)	81.5 (79.9)	86.9 (87.8)	97.4 (101.9)
Time since nAMD diagnosis (mo)					
Mean (SD)	3.4 (2.0)	3.2 (1.5)	3.9 (2.1)	3.4 (1.8)	3.5 (1.9)
Median	2.5	2.5	3.1	2.3	2.7
Range	1.0–10.5	1.0–7.6	1.9–10.2	1.3–8.6	1.0–10.5

2

BCVA = best-corrected visual acuity; CFT = central foveal thickness; ETDRS = Early Treatment Diabetic Retinopathy Study; ILM = inner limiting membrane; nAMD = neovascular age-related macular degeneration; PDS = Port Delivery System with ranibizumab; PED = pigment epithelial detachment; RPE = retinal pigment epithelium; SD = standard deviation; VEGF = vascular endothelial growth factor.

Observed data, modified intent-to-treat population (N = 220).

Table 2. Time to First Implant Refill in Port Delivery System with Ranibizumab Treatment Arms, Modified Intent-to-Treat Population

	PDS Ranibizumab 10 mg/mL (n = 58)	**PDS Ranibizumab 40 mg/mL (n = 62)**	**PDS Ranibizumab 100 mg/mL (n = 59)**
Incidence of first implant refill			
Patients who required first implant refill at time of primary analysis, n (%)	37 (63.8%)	29 (46.8%)	27 (45.8%)
Time to first implant refill (mo)			
Median (80% CI)	8.7 (7.1–9.8)	13.0 (11.8–NE)	15.0 (11.9–16.9)
Range	0.3*–29.7*	1.0*–24.6*	0.9*–30.3*
Stratified survival analysis			
Compared with PDS 10 mg/mL			
P value (log-rank test)		0.0415	0.0066
Hazard ratio (70% CI)		0.60 (0.46–0.78)	0.50 (0.38–0.66)
Compared with PDS 40 mg/mL			
P value (log-rank test)			0.7523
Hazard ratio (70% CI)			0.92 (0.69–1.22)
Unstratified survival analysis			
Compared with PDS 10 mg/mL			
P value (log-rank test)		0.0360	0.0185
Hazard ratio (70% CI)		0.60 (0.46–0.77)	0.55 (0.43–0.72)
Compared with PDS 40 mg/mL			
P value (log-rank test)			0.9010
Hazard ratio (70% CI)			0.97 (0.73–1.28)

CI = confidence interval; NE = not evaluable; PDS = Port Delivery System with ranibizumab. Stratified log-rank test at a 1-sided significance level of 15%. The stratification factors were baseline best-corrected visual acuity (BCVA) score (≤ 65 Early Treatment Diabetic Retinopathy Study [ETDRS] letters vs. ≥ 66 ETDRS letters) and baseline number of prior anti−vascular endothelial growth factor (VEGF) intravitreal injections (≤ 3 injections vs. ≥ 4 injections). The hazard ratio for each pairwise comparison of the treatment arms was

estimated using a Cox proportional hazards regression model stratified by baseline BCVA score (≤ 65 ETDRS letters vs. ≥ 66 ETDRS letters) and number of prior anti-VEGF intravitreal injections (≤ 3 injections vs. ≥ 4 injections) with main effects for treatment. The censoring date was defined as the date of a patient's last visit before the cutoff date or the date when the patient discontinued from the study, whichever occurred first. Time to first refill was also censored for the following patients: 1) at the time of an intravitreal anti-VEGF injection in study eye if administered before the first required refill; 2) at the time the refill criteria could not be assessed, defined as when ≥ 2 refill variables (BCVA, central foveal thickness, or new macular hemorrhage) could not be evaluated for any reason, or were affected by a clinical reason different from neovascular age-related degeneration activity, before the first required refill; and 3) at the time of implant explant.

*Censored data.

Table 3. Treatment Exposure for Safety-Evaluable Population

	PDS Ranibizumab 10 mg/mL (n = 58)	PDS Ranibizumab 40 mg/mL (n = 62)	PDS Ranibizumab 100 mg/mL (n = 59)	All PDS Patients (n = 179)	Monthly Intravitreal Ranibizumab 0.5 mg (n = 41)
Overall time on study at time of primary analysis (mo)					
Mean (SD)	16.9 (6.2)	17.0 (6.0)	16.4 (5.8)	16.8 (6.0)	16.4 (6.8)
Median	14.8	15.6	14.7	15.0	14.4
Range	10.2–32.2	10.2–33.0	9.8–32.6	9.8–33.0	7.0–30.7
No. of ranibizumab treatments per patient*					
Mean (SD)	3.7 (6.7)	2.6 (2.3)	2.4 (1.9)	2.9 (2.6)	16.8 (6.7)
Median	2	1	2	2	15
Range	1.0–16.0	1.0–10.0	1.0–9.0	1.0–16.0	7.0–31.0
Study eye, n (%)					
Received any rescue intravitreal ranibizumab†	13 (22.4%)	3 (4.8%)	6 (10.2%)	22 (12.3%)	NA
Met lack of clinical efficacy criteria	13 (22.4%)	3 (4.8%)	1 (1.7%)	17 (9.5%)	0
Met lack of clinical efficacy criteria and received rescue PDS 100 mg/mL refill	10 (17.2%)	1 (1.6%)	0	11 (6.1%)	NA

NA = not applicable; PDS = Port Delivery System with ranibizumab; SD = standard deviation.

Observed data; safety-evaluable population.

*Total number of ranibizumab treatments includes both implant refills and any rescue treatments.

†In the PDS 10 mg/mL, 40 mg/mL, and 100 mg/mL arms, 2 of 13, 0 of 3, and 2 of 6 patients, respectively, received rescue treatment because implant refill criteria could not be assessed due to vitreous hemorrhage.

Table 4. Port Delivery System with Ranibizumab–Associated Adverse Events for Safety-Evaluable Population

	PDS Ranibizumab 10 mg/mL (n = 58)		**PDS Ranibizumab 40 mg/mL (n = 62)**		**PDS Ranibizumab 100 mg/mL (n = 59)**		**All PDS Patients (n = 179)**	
	Time from Surgery		*Time from Surgery*		*Time from Surgery*		*Time from Surgery*	
Patient Incidence, n (%)	**≤ 1 Mo**	**> 1 Mo**	**≤ 1 Mo**	**> 1 Mo**	**≤ 1 Mo**	**> 1 Mo**	**≤ 1 Mo**	**> 1 Mo**
Eye disorders								
Vitreous hemorrhage before May 2016, procedure update	6/10 (60.0%)	0	2/7 (28.6%)	0	3/5 (60.0%)	0	11/22 (50.0%)	0
Vitreous hemorrhage after May 2016, procedure update	0/48 (0%)	1/48 (2.1%)	3/55 (5.5%)	1/55 (1.8%)	2/54 (3.7%)	0	5/157 (3.2%)	2/157 (1.3%)
Cataract, all types*	0	1 (1.7%)	0	4 (6.5%)	0	8 (13.6%)	0	13 (7.3%)
Conjunctival bleb	3 (5.2%)	0	2 (3.2%)	1 (1.6%)	0	0	5 (2.8%)	1 (0.6%)
Conjunctival erosion	0	1 (1.7%)	0	2 (3.2%)	1 (1.7%)	1 (1.7%)	1 (0.6%)	4 (2.2%)
Rhegmatogenous retinal detachment	1 (1.7%)	1 (1.7%)	0	1 (1.6%)	0	1 (1.7%)	1 (0.6%)	3 (1.7%)
Tractional retinal detachment	0	1 (1.7%)	0	0	0	0	0	1 (0.6%)
Infections and infestations								
Endophthalmitis	1 (1.7%)	0	0	1 (1.6%)	0	1 (1.7%)	1 (0.6%)	2 (1.1%)
Injury, poisoning, and procedural complications								
Hyphema	2 (3.4%)	2 (3.4%)	1 (1.6%)	0	3 (5.1%)	0	6 (3.4%)	2 (1.1%)
Conjunctival retraction	0	0	1 (1.6%)	1 (1.6%)	1 (1.7%)	0	2 (1.1%)	1 (0.6%)
Conjunctival filtering bleb leak	0	0	1 (1.6%)	0	0	0	1 (0.6%)	0

Observed data, safety-evaluable population. Month 1 visit included data up to 37 days. At the time of the primary analysis, no Port Delivery System with ranibizumab (PDS) patients reported any the remaining protocol-specified PDS-associated adverse events: vitreous hemorrhage associated with a > 30 Early Treatment Diabetic Retinopathy (ETDRS) letter decrease of best-corrected visual acuity (BCVA) compared with the last assessment of BCVA before the onset of vitreous hemorrhage lasting > 1 month, > 30 ETDRS letters BCVA loss from previous scheduled visit, scleral damage, and interference of the implant in the visual field.

*Proportion of phakic patients at baseline was similar across treatment arms; in the monthly intravitreal ranibizumab 0.5 mg injection arm, the incidence of cataract was 3 (7.3%) for onset > 1 month and 0 for onset ≤ 1 month.

Figure 1. Port Delivery System with Ranibizumab Implant

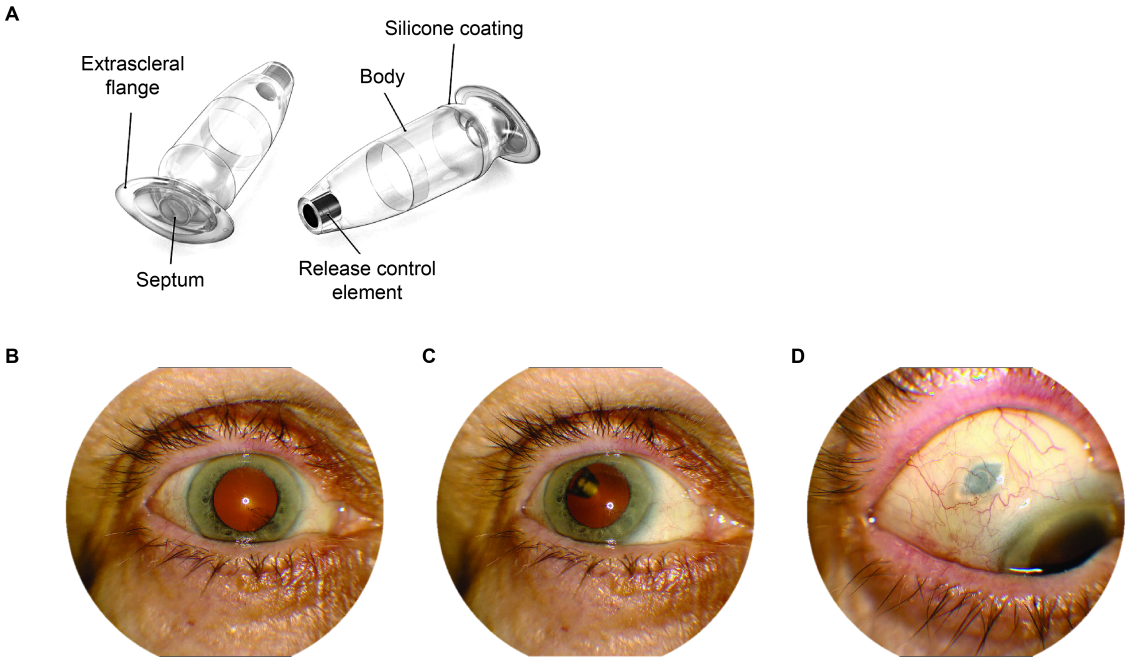


Figure 2. Time to First Implant Refill, Modified Intent-to-Treat Population

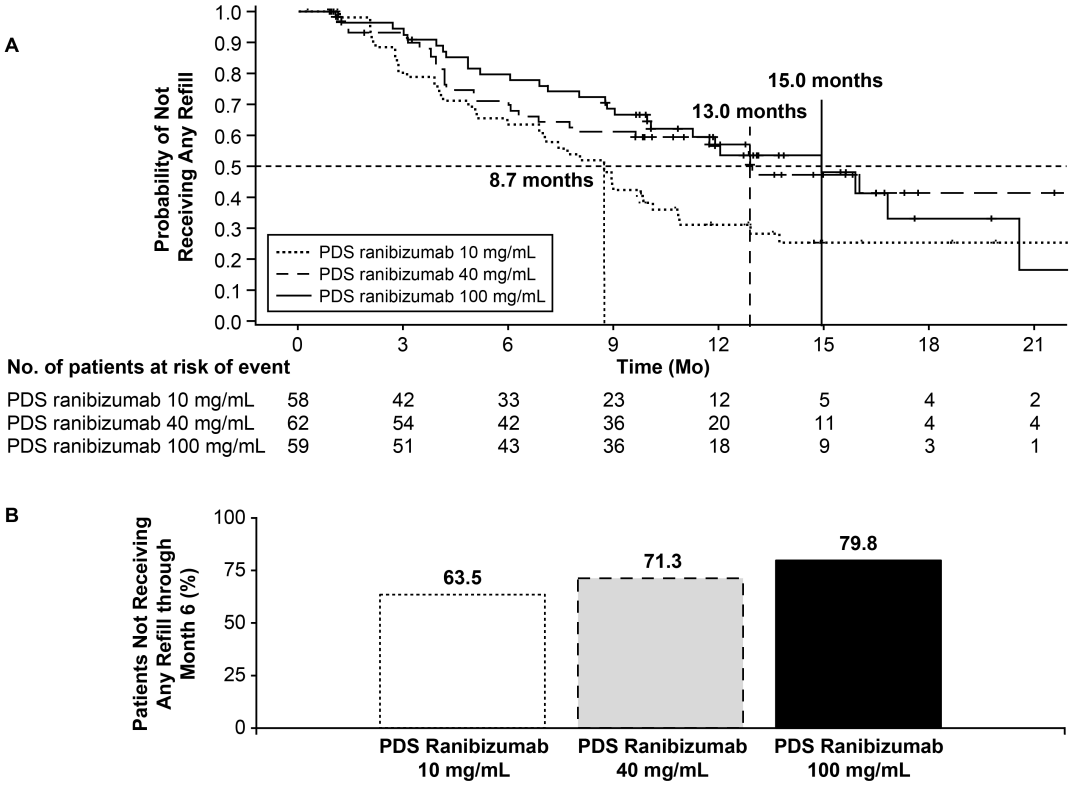


Figure 3. Adjusted Mean Best-Corrected Visual Acuity Change from Baseline, Modified Intent-to-Treat Population

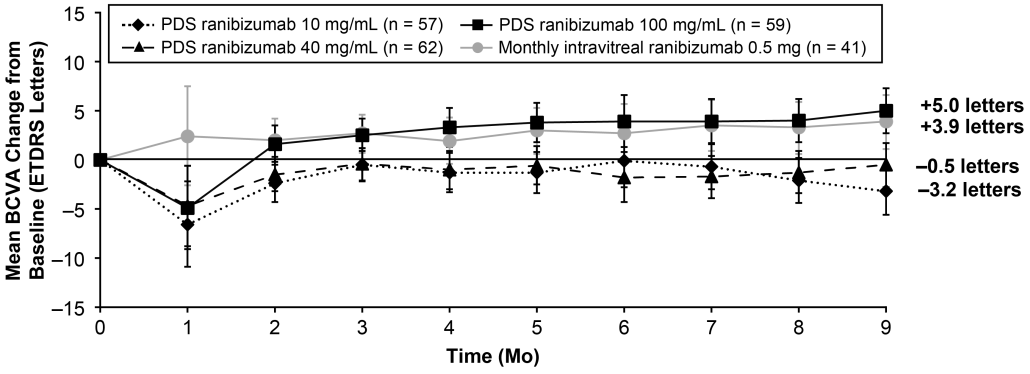
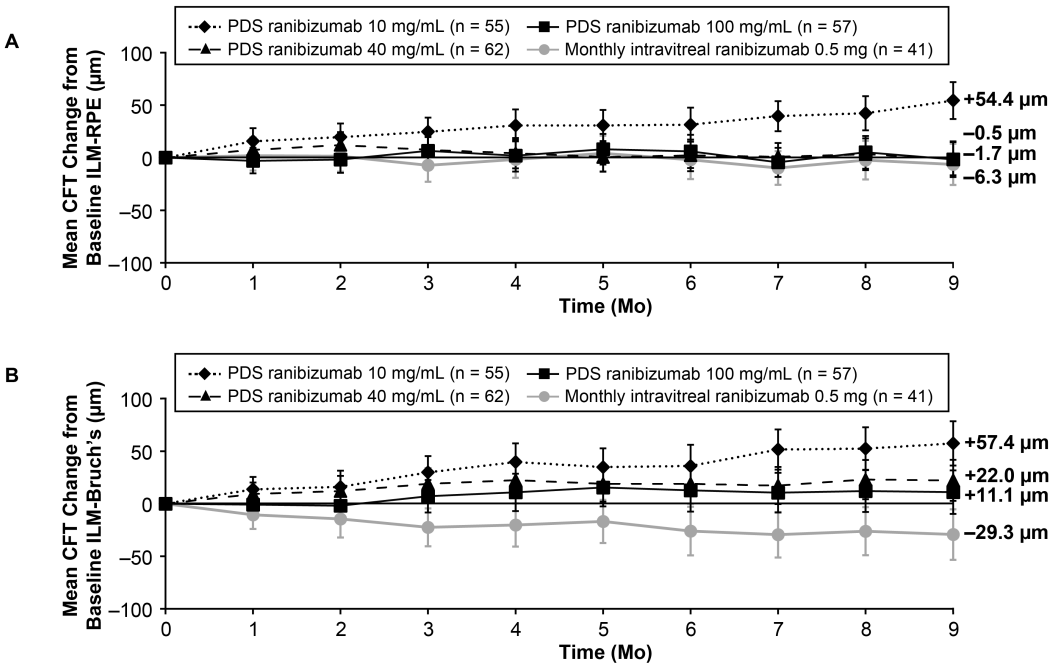


Figure 4. Adjusted Mean Central Foveal Thickness Change from Baseline, Modified Intent-to-Treat Population



Précis: The phase 2 Ladder trial met its primary endpoint and demonstrated the safety and efficacy of the Port Delivery System with ranibizumab for the treatment of neovascular age-related macular degeneration.